HDBuzz

Huntington's disease research news. In plain language. Written by scientists. For the global HD community.

Buzzilia Video: Day 1

Buzzilia video: Day 1. Highlights of the 2013 HD World Congress in Brazil: nightly news, interviews and features

By Dr Jeff Carroll on October 09, 2013
Edited by Dr Ed Wild

We present Buzzilia, video 1: news highlights and in-depth interviews with top HD researchers from the World Congress on Huntington's disease 2013 in Rio de Janeiro. On the opening day of the Congress, Jeff and Ed review the major developments since the last World Congress in 2011, and talk to Prof Elena Cattaneo from Milan, Italy, about the huntingtin protein.

The full unedited video (50 minutes), including our fun 'Generation Game' quiz and a special appearance from Charles Sabine, can be found on YouTube.

[Samba music]

ED: The last Congress was two years ago in Melbourne, Australia. We wanted to step back a little, take a bit of an overview. Figure out where we are, why we're here, where we're going, and then, as the sessions go on, we'll fill in with some specifics. So, what we want to do is start with five big reasons to have hope, if you're a family member, or if you're someone affected by Huntington's disease.

JEFF: Ed and I spend a lot of time talking to patient groups around the world, trying to spread something we call 'substantive hope'. Which is not the hope that 'they' — it's always 'they' are working on Huntington's disease, 'they' are working on developing treatments — real people, in real labs are working hard, around the clock, trying to help therapies for this disease. So we want to share with you our personally picked, from many, top five reasons for being hopeful about Huntington's disease, now.

ED: The first one is a slightly controversial statement. I've said this many times at patient family meetings, and so far, I've never been lynched. Huntington's disease, in my mind, and Jeff kind of agrees, is the most curable incurable brain disorder. What I mean by that is that, because we know what genetic mutation causes Huntington's disease, we know exactly what the problem is. Everyone with HD has the same basic genetic mutation. Everyone with that mutation will get Huntington's disease, unless we can do something about it. What that gives us is an opportunity that many other diseases don't have. Alzheimer's, Parkinson's disease: they don't know, in the vast majority of cases, what causes that disease in a particular person. In Huntington's disease, we know that we have to sort out this mutation, sort out the protein that it produces, and that will work in treating Huntington's disease. So, it is incurable, but we in the HD research community, believe that it should be curable, if we can work hard enough, together.

JEFF: Next, the global community of HD organisations, both research and patient focused. These organisations are local, as we've heard about today. Helping people in specific regions and countries, but global and

networking to share information that will help, not only the care of Huntington's patients, but ultimately to develop the trials that will lead to effective therapies for Huntington's disease. I don't know if you people know this, but organising scientists is kind of a thankless task. They tend to be an independent bunch, and the infrastructure that has been established for these networks has gone a long way towards making this work, more effectively.

ED: The third, big reason to have hope is something I call the 'golden window of opportunity'. The basic idea here is that someone with the genetic mutation that causes Huntington's, unless we can do something about it, will get signs of the disease, or symptoms of the disease, at some point. 'Symptom onset', we call that. We know that that's associated with a mixture of neurons in the brain that are struggling — they're unhappy, but they're not dead — and later on in the disease, those neurons die prematurely. In this window, where the neurons are struggling, but not dying, that's the 'golden window', where we believe that we can intervene to keep those neurons happier, make things a little bit easier for them. The availability of the genetic test means that we can study people, and hopefully, when we have treatments, we can hopefully treat people before symptom onset, and push that symptom onset later. Hopefully, we can do that a little bit at first, and then more and more, and hopefully make an impact on this disease.

JEFF: Having symptoms doesn't mean it's too late. Patients often ask, "If I'm already symptomatic can these treatments you're talking about developing have any impact on my disease?" Of course, we don't know the answer to this until we run definitive clinical trials, but we think there are good scientific reasons for having hope. In particular, a relatively old, at this stage, experiment that was done with a bit of genetic trickery, in which a mouse was born with a mutant copy of an HD gene, which, of course, like people, makes it sick. So the mouse is born with these gene, it gets sick. What we can do in mice, but not people, is have a genetic trick that lets us

now turn that gene off. So we made the mouse sick, like an HD patient, in some ways, and then we turn off the gene. What happens? Not only do they stop getting sicker, they seem to get better. Almost as if all the brain needed was a break from the onslaught of toxicity from this mutant gene, and we just need to give it a little holiday. In that holiday, the brain, at least in mice, seems capable of healing itself. So, we think there's a good reason to believe that we could help somebody's brain, even if they were symptomatic.

ED: Our final big reason to have hope is a slightly philosophical one. I like to think of science as being a bit like a glacier, or if you're English, a 'glassier', and you can laugh at whichever one of those you like. With a glacier, snowflakes fall on top of a mountain, and no one snowflake makes a big difference, but over the years and over the decades, they are compacted together into this huge structure, that can literally move mountains. Science is the same. Not only can science move mountains if we try hard enough, we also know that the snowflakes are falling all the time. Every day, we know a bit more than we did the day before. When half the world's scientists are asleep, the other half are awake and working on Huntington's disease. So, having given you our five big reasons to have hope, what has happened in the past two years? The last World Congress was two years ago. What are some notable advances that have happened? We've chosen just a tiny handful from lots and lots of things that we could have mentioned, and we'll certainly hear about more, this week.

JEFF: We think there's a lot to be optimistic about. One big advance in the last two years has been the advance of so called 'gene silencing' as a therapy for HD. It's a remarkable technology that basically let's you turn off any particular gene, you want. Because all this bad stuff in Huntington's disease patients happens because of this mutant gene, which we know, as Ed said, getting rid of that gene is a pretty attractive idea, as a therapy. Everything bad that happens in HD stems from that gene. If we could just

turn it off… Gene silencing has been advancing rapidly, over the last decade. This year Isis Pharmaceuticals published the results of a safety trial in familial ALS, another nerve degenerative disease, showing that they could infuse similar silencing drugs to the ones we'll need in Huntington's disease into the central nervous system of patients, with no adverse events. That's a huge finding; it opens up the pathway to the brain.

ED: In case you think that's too academic and too remote from Huntington's disease, get this. Earlier this year, the massive drug company, Roche, announced that they were investing in Isis and their Huntington's disease gene silencing programme to the tune of $32m immediate investment, and up to $360m more, for the final push to bring these drugs to a clinical trial. This was our reaction, when we heard that news, and we suggest that you react similarly.

JEFF: This year, the final major publications from Track HD were published, an observational study of human HD mutation carriers. The Predict HD study continued its work, observing people who carry the HD mutation, but don't yet have symptoms. Some of those people have been observed for over ten years, now. This kind of data is critical to planning good clinical trials. No one now can say now, "We're not ready to run clinical trials in HD". Because of these studies, we know so much about how this disease process progresses in people.

ED: This is something that we've heard a little bit about today. There's actually a spelling mistake on this slide, which will become very ironic, in a few minutes. So, we heard a little bit about phosphodiesterase inhibitors. These are drugs which affect the working of a molecular machine, which crunches up signalling molecules. We believe that may be helpful for making the brain work better in Huntington's disease. Earlier on, CHDI and Pfizer, who are working together, announced some really encouraging results, which we'll be hearing about, shortly. At least two other companies are developing drugs that do something similar. So, not only do we have

big drug companies working on Huntington's disease, but they're also, in some cases, racing to the finish line, to try and perfect their drugs, and test them. Which is great news.

JEFF: Another exciting piece of news this year was that a long time Huntington's disease researcher, and incidentally my science dad, Michael Hayden - shown here in full Rio mode, which I'm sure he appreciates - had joined Teva Pharmaceuticals, a major pharmaceutical company, where he's their head of research. So now, of course, Teva is a large pharmaceutical company, they work on a number of diseases, but one of the first things they announced, once Michael joined them, was the acquisition of a very advanced HD drug candidate. So nobody can say we don't have friends in pharma, anymore.

ED: So, that's our five big reasons to have hope and a few exciting things. As I said there are many more, and we'll hear more about them as the week goes on, and new stuff that we can't even begin to imagine, yet. [music]

JEFF: Please join me in welcoming Professor Elena Cattaneo from the University of Milan. Elena, you get the whole couch to yourself.

ED: You should feel free to recline.

JEFF: The highlight of this interview is that Ed has to give his mic to Elena, so now we can all enjoy our peaceful evening. So, thank you for agreeing to be our guinea pig, thank you for agreeing to talk about your work with the Huntingtin gene, in ways hopefully, that people at home can understand. Today you were talking about the Huntingtin gene in not just mice, and flies, and worms, and people, but in a range of organisms. Just what kinds of organisms have Huntingtin? What's the oldest organism that has a Huntingtin gene?

ELENA: The most ancient organism is an amoeba. The name is Dictyostelium discoideum, and it is the first pluricellular organism that has appeared. Of course, when the gene was born in this species, it was born with no CAG repeat, but the gene is there.

ED: What's a CAG repeat?

JEFF: Who gave that man a microphone?

ELENA: It's just a series of letters that appear in the gene, but based on these studies that have been conducted by people in this audience, we know that when the gene was born - and this was 800 million years ago.

ED: 800 million years ago? That was when the Huntingtin gene first appeared?

ELENA: Yes. It was basically born with no CAG, so these letters were not there. The other thing that is very interesting is that this species is the first pluricellular organism.

JEFF: What's a pluricellular organism?

ELENA: It's an organism composed by multiple cells together, they have to talk to each other. Before this organism, we have unicellular organisms, like yeast. So they are individual cells. These individual cells do not have Huntingtin. Then, you have the first pluricellular organism, which is this amoeba, Dictyostelium discoideum, and this species, this amoeba, has the Huntingtin gene. The gene is there in an 'innocent' form, with no CAG repeats.

JEFF: So it's only when the cells got social, in a way — when they started sticking together — that they had to have a Huntingtin gene?

ELENA: Yes, so maybe we should think about this idea of the gene being a social gene, so a good gene, at the beginning of the evolution. So the gene was born without CAG repeats. Then, as you know, evolution basically develops in two different branches. One is the protostome

branch, for example, insects belong to the protostome branch. The other is deuterostome branch, and we belong to the deuterostome branch. We know that, of course, the gene was passed to the other species, but then only in the deuterostome branch, the CAG has appeared.

ED: So from the amoeba onwards, every animal has Huntingtin, but in the branch of the animals that contains flies and insects, they have Huntingtin, but no CAG?

ELENA: Exactly.

ED: And in the branch that contains people, CAGs start to appear?

ELENA: Exactly. So this is why we should think of these letters, that suddenly appear in the gene, as an acquisition of the deuterostome branch. This acquisition was not there just by chance in one species and then disappeared – it has remained in there. This is, I think, telling us something very important.

JEFF: So it's useful, in some way?

ELENA: It is there, exactly, so when the CAG appears in the deuterostome branch, in the first species, which is sea urchin. The incredible thing is that these CAG repeats, and they first appear in two CAG repeats. The sea urchin Huntingtin has two CAG repeats. These CAG repeats are positioned exactly at the same position where the CAG is in my gene. So it's not random in the gene. So, they appear just a few, a couple, in sea urchin. Very good to eat, but this is also the first species that has a very primitive nervous system. So this is another message. Of course, we are dreaming now, because we like to dream and imagine how things can be. Then, you go to the lab to verify whether this is wrong, or not. Or whether this is true, or not. We are thinking that maybe the appearance of the CAG in sea urchin Huntingtin probably has instructed the appearance of the first elements of the very primitive nervous system. Then, this CAG repeat didn't disappear in the other species, so they remained there. The

incredible thing is that they kept growing in number. So you have more evolved species, or species with a more evolved, more complex, nervous system, have a progressively higher number of CAG repeats. This is very progressive. It's not sudden. This is just amazing.

ED: As we know, Huntington's disease happens in people when there are more than the regular number of CAG repeats. So, everyone has two copies of the HD gene, and someone who's gong to get Huntington's disease will have a larger number than usual of CAG repeats. So this thing that has been growing and growing over millions and millions of years, in people who have Huntington's, or who are going to get it, it sounds like that process of growing has just gone a little bit too far. Something that was really useful, and seems to be doing something really good, because it's growing over evolutionary time, seems to have just gone a little bit further than is healthy, right?

ELENA: Yes, but I think the first message, again maybe this is just philosophical, but the first message is that we can extract from this information is that the CAG repeat is part of our evolution. It is something important, and patients belong to this evolution, too. So they are not something aside. Why this good process in some way got too far away? Of course, we don't know, but there are data, also from Michael Hayden, and also from other colleagues, really showing that even in normal people, evolution keeps pushing to want more CAG repeats, and more CAG repeats. So, we know that we are polymorphic. Normal subjects for that gene are polymorphic.

ED: When you say we're polymorphic, you mean we have a range of different CAG repeat lengths?

ELENA: I would say we have the gene with different 'flavours' of CAG repeats. So I can have 10, you can have 12, another can have 15. We have the same gene in different flavours. So what we learn from the studies that people have conducted, is that evolution, in normal subjects,

keeps pushing toward more CAG. So probably none of us is nine, or at least I hope. So there are a lot of people that have a high number of CAG repeats, within the normal range. This is another important message; there is an interesting paper that was published in 2011, by a German Group, they are clinicians. They have conducted MRI scans on 300 normal subjects. To summarise the message from their work, the message is the following one. They found that the people that have more CAG repeats in the normal range, are also the people, based on their MRI scan, that have more grey matter. So more CAG repeats in the normal range maybe means, I don't know, more neurons, more circuitries. I don't know whether it means more intelligence. Maybe it means being more friendly, or being more social, or more funny, I don't know. This is telling us something, and this is a good trait, and there is more brain if you have more CAG repeat. Probably, in the diseased state, our neurons are not able to cope with larger CAG repeat. Instead of using them to obtain a benefit, of course, if you are not able to cope with these growing CAG repeats, then you have the disease. So we just have to exercise our neurons, to take advantage of larger CAG repeats.

ED: It's really fascinating stuff. I think we have to leave it there, Elena. This is a protein that keeps on surprising us.

JEFF: As a slight aside, but something that's important to us, we wanted to highlight, as she leaves, Elena's recent appointment as a Life Senator in her native Italy. In fact, I think, only the third woman ever to be appointed, yes? So, the fight against Huntington's disease is not only a scientific war, but a war of human rights, and Elena is really at the forefront of that. I think, as she returns to her seat, we should recognise her. Thank you Elena. [Applause]

The authors have no conflicts of interest to declare. For more information about our disclosure policy see our FAQ...

Glossary

Parkinson's Disease A neurodegenerative disease that, like HD, involves motor coordination problems

huntingtin protein The protein produced by the HD gene.

Phosphodiesterase a protein that breaks down cyclic-AMP and cyclic-GMP

gene silencing An approach to treating HD that uses targeted molecules to tell cells not to produce the harmful huntingtin protein

observational A study in which measurements are made in human volunteers but no experimental drug or treatment is given

CAG repeat The stretch of DNA at the beginning of the HD gene, which contains the sequence CAG repeated many times, and is abnormally long in people who will develop HD

neuron Brain cells that store and transmit information

magnetic resonance A technique using powerful magnetic fields to produce detailed images of the brain in living humans and animals

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